## Remarks

Errata

The sequence now designated as SEQ ID NO: 5 has been corrected so that it matches the description in the text, *i.e.,* the first six codons of *hPMS2*, as shown in SEQ ID NO: 1. Sequence identifiers have been added to page 19 of the specification.

Previously in the prosecution of this application factual declarations were submitted in support of patentability. They were designated as declarations under rule 131. In fact, they appear to be rule 132-type declarations, as they do not pertain to proving a date of invention prior to a cited reference.

Priority

The priority statement has been amended to update the status of the parent application.

Sequence Compliance

The application has been amended to provide sequences and sequence identifiers for the recited sequences on page 19 of the specification. A paper form and computer readable form of a substitute sequence listing accompany this submission. The content of the two forms is believed to be identical. The substitute sequence listing adds no new matter to the application.

Substantial Duplicates

Claim pairs 81 and 82, 88 and 89, and 91 and 92 were identified as patentably indistinct. Base claims 60, 62, and 71, from which the claim pairs depend, have been amended to delete the recitation of the *PMS2-134* allele. It is respectfully submitted that these amendments render each member of the claim pairs distinct.

The Rejection of Claims Under 35 U.S.C. § 112, ¶ 1

***New matter***

Claims 60-62 and 71-75 stand rejected as failing to comply with the written description requirement. The new recitation in claims 60-62 and 71 of "a PMS2-134 allele" is said to be new matter not supported by the specification. The specification at page 7 is said to teach only "dominant negative alleles of a mismatch repair gene [that] can be obtained from cells of humans, animals, yeast, bacteria or other organisms." The only *PMS2-134* allele that is allegedly taught in the specification is the human allele. The disclosure of the single species of human *PMS2-134* allele is said not to adequately support the genus of *PMS2-134* alleles from any species.

The offending recitation has been removed and replaced with a recitation that the PTO acknowledges is supported. (See page 5, lines 4-6 of the Office Action.) The claims have been amended to recite a dominant negative allele of a mismatch repair gene.

This recitation is fully supported in the specification as filed. For example, the specification teaches that expression of a dominant negative allele of a mismatch repair gene inhibits mismatch repair activity, thereby causing the cells to accumulate mutations at an abnormally high rate (*i.e.,* the cells become hypermutable). (Specification at page 7, lines 7-9.) The specification further describes reliable indicators of the phenotype and identifies various assays enabling one of skill in the art to assess mutagenesis. (Specification at page 10, lines 15-24.) The Declaration of Dr. Nicolaides (dated June 17, 2003) establishes that it was well within the skill of the ordinarily skilled artisan to identify dominant negative forms of a *PMS2* mismatch repair gene *in vitro*. One skilled in the art would have understood that, just as

dominant negative forms of a *PMS2* mismatch repair gene from species other than human can be readily substituted for human *PMS2-134* to induce hypermutability *in vitro* as established by Dr. Nicolaides, dominant negative forms of a *PMS2* mismatch repair gene from species other than human can be readily substituted for human *PMS2-134* as employed in the hypermutable mouse described by Dr. Kline (declarations dated September 16, 2002 and April 17, 2003).

Withdrawal of this rejection is respectfully requested, as the offending alleged new matter has been deleted from the claims.

***Enablement***

Claims 60-62, 71-75, and 81-96 are rejected as not supported by an enabling disclosure for their full scope. Specifically, enablement is said to be limited to transgenic mice that express human PMS2-134 protein in all germ and somatic cells and wherein that protein is encoded by the transgene.

The claims have been amended to conform to the scope that the examiner acknowledges is enabled.

The Office Action asserts that "the specification has not taught that the PMS2 gene from a non-human species will have a dominant negative effect when truncated at amino acid 133." (Office Action at page 8.) The claims are amended herein to clarify that the genus of polynucleotides recited encompasses dominant negative forms of a *PMS2* gene. One skilled in the art armed with the present specification and the knowledge in the art would have been able to practice the claimed invention without undue experimentation.

As taught in the specification at page 6, lines 21-23, the process of mismatch repair is carried out by protein complexes in cells from species ranging from bacteria to mammalian cells. Expression of polynucleotides comprising dominant negative forms of a mismatch repair gene

causes hypermutability even in the presence of a wild-type allele. (Specification at page 7, lines 1-2.) Dominant negative alleles of a mismatch repair gene can be obtained from the cells of humans, animals, yeast, or bacteria. (Specification at page 7, lines 13-14.) Expression of a polynucleotide comprising a dominant negative form of a mismatch repair gene in a cell or an animal will cause hypermutability. (Specification at page 7, lines 28-29.) One skilled in the art would have been able to identify polynucleotides comprising dominant negative forms of *PMS2* mismatch repair genes by using PMS2 from other species in place of human PMS2-134, and by using the teachings of the specification to determine whether the PMS2 induces hypermutability.

Applicants have provided substantial guidance in the specification for identifying polynucleotides comprising dominant negative forms of *PMS2* mismatch repair genes. For example, the specification teaches that expression of a dominant negative allele of a mismatch repair gene inhibits mismatch repair activity, thereby causing the cells to accumulate mutations at an abnormally high rate (*i.e.,* the cells become hypermutable). (Specification at page 7, lines 7-9.) The specification further describes reliable indicators of the phenotype and identifies various assays enabling one of skill in the art to assess mutagenesis. (Specification at page 10, lines 15-24.) The Declaration of Dr. Nicolaides establishes that it was well within the skill of the ordinarily skilled artisan to identify dominant negative forms of a *PMS2* mismatch repair gene from other species. Just as other dominant negative forms of a *PMS2* mismatch repair gene can be substituted for human *PMS2-134* to induce hypermutability *in vitro* as described in Dr. Nicolaides' declaration, other dominant negative forms of a *PMS2* mismatch repair gene can be substituted for the human *PMS2-134* employed in the hypermutable mouse exemplified in Dr. Kline's declarations. In view of the evidence of record, one of ordinary skill in the art would predict the expect species other than humans to have or be inducible to have dominant negative

forms of a *PMS2* mismatch repair gene. One of ordinary skill in the art would further expect such dominant negative forms to function in a mouse or fertilized mouse egg. The Declarations of Dr. Kline demonstrate that one of skill in the art could readily identify transgenic animals having a hypermutable phenotype, for example, by detecting microsatellite instability.

Enablement requires that the ordinarily skilled artisan be able to make and use the invention without recourse to undue experimentation. Because human *PMS2-134* and its plant homolog produce a dominant negative phenotype in cells, one of skill in the art would have expected dominant negative forms of a *PMS2* mismatch repair gene of other species to also produce a dominant negative phenotype. One of ordinary skill in the art could readily use such dominant negative forms to make transgenic mice using techniques known in the art. Applicants have taught how to make hypermutable, transgenic mice having polynucleotides comprising dominant negative forms of PMS2 mismatch repair proteins; those of ordinary skill in the art could readily and successfully follow these teachings without recourse to undue experimentation. Applicants have therefore enabled the full scope of the invention as now recited.

Withdrawal of this rejection is respectfully requested.

The Rejection of claims 60-62, 71-75, and 81-96 under 35 USC § 112, second paragraph

Claims 60-62, 71-75, and 81-96 stand rejected under 35 USC § 112, second paragraph, for failing to be definite. This rejection is respectfully traversed.

Recitations encompassing non-human PMS-134 proteins were said to be unclear. Recitation of these proteins has been deleted from the claims.

The term "allele" was said to be unclear when used to describe a transgene. The term has been deleted from the claims.

The prepositional phrase preceding recitations of "SEQ ID NO: 1" was said to be unclear. The prepositional phrase has been amended as suggested by the examiner to clarify the intended meaning. Applicants respectfully request withdrawal of the rejection for lack of clarity.

All issues, objections, and rejections of the office action have been addressed. It is respectfully urged that the claims are now in condition for allowance. Should there be any remaining issues, the examiner is invited to contact the undersigned directly.

Respectfully submitted,
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Date: March 9, 2006

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